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The effect of growth factors on the osseointegration of dental implants

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Dissertação Orientada
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Dissertação

Mestrado Integrado em Medicina Dentária

2017

ACKNOWLEDGEMENTS

To Prof. Dr. João Caramês and Prof. Dra. Helena Francisco, for the kindness, commitment and guidance.

To my parents and grandmother, for helping me reach for the stars.

To my sister, for being my other half.

To Carlota, for teaching the true definition of friendship.

To Diana, Joana and Rita, for lighting up my life, with laughs, love and food.

To Inês, for all the travel plans, concerts and Norwegian tv shows.

To all my colleagues and teachers at university, for all the knowledge and patience.

ABSTRACT

Introduction: Dental implants have been an option of treatment commonly used in dentistry. Osseointegration is a measure of implant stability and can be enhanced by increasing the contact of bone to implant. Many strategies such as osteogenic coatings with growth factors have been studied in order to achieve it.

Objective: To evaluate the effect of growth factors coating dental implants on the osseointegration.

Methods: An electronic search was conducted in three databases such as PubMed, Evidence Based-Dentistry and Cochrane Library with the keywords "growth factors AND osseointegration AND dental implants", "bone morphogenetic protein AND osseointegration AND dental implants", "platelet derived growth factor AND osseointegration AND dental implants", during November 2016 and May 2017. There were included in vivo studies that evaluated the effect of growth factor coated implants on maxillae or mandibular bone. Articles were limited to those published in English, Portuguese and Spanish.

Results: Nine animal studies were analysed according to their results and surface modification. Five articles revealed a positive effect on the osseointegration, as the values obtained were higher when compared to uncoated groups. The lack of standardization makes the comparison of studies and their analysis difficult and therefore it is not possible to conclude the real action of these proteins on the formation of bone.

Conclusions: New therapies have been developed to increase the contact between bone and implant and its stability by altering their surfaces. Implants coated with growth factors seem to be a promising alternative to increase the rate of long term successful implant surgeries and needs to be assessed in order to become an available option for future treatments. It is crucial the creation of prospective studies to extrapolate these results to a human model.

Key words: growth factor, dental implant, osseointegration, bone morphogenetic protein, platelet derived growth factor

RESUMO

Introdução: A colocação de implantes tem sido uma opção de tratamento cada vez mais aceite na comunidade científica para a reabilitação oral de pacientes total ou parcialmente edêntulos. A literatura descreve taxas de cerca de noventa e cinco por cento de sucesso em estudos de longa duração. Esta nova modalidade deve-se à capacidade dos implantes de se ancorarem no osso, levando a um contacto próximo entre o mesmo e a superfície do implante. Esta relação leva a uma cascata de eventos, regulada por células sanguíneas, que permite a cicatrização dos tecidos envolventes, formação de tecido conjuntivo e osso. Consequentemente, observa-se a uma maior taxa de osteointegração, sucesso e previsibilidade de tratamento. Estes parâmetros são avaliados através da estabilidade dos implantes que pode ser medida com recurso a métodos invasivos ou não invasivos. A literatura tem descrito a influência das superfícies dos implantes na diferenciação celular e na produção de fatores locais. Após cirurgia, o implante entra em contacto com diversas proteínas e tipos celulares que permitem a formação de osso. Esta relação estrutural é essencial para prevenir a formação de fluido periimplantar que aumenta o risco de infeção e de falha do tratamento com implantes. Nesse sentido, várias estratégias têm sido desenvolvidas ao nível da topografia dos implantes para promover a osteointegração e mimetizar as características do osso, nomeadamente a colocação de fatores de crescimento na superfície. Estes fatores têm sido definidos como agentes promotores da proliferação e metabolismo celular, uma vez que induzem a migração e recrutamento de células responsáveis pelo processo de cicatrização e osteogénese. Adicionalmente, são responsáveis pela diferenciação e divisão tecidular e síntese de matriz. Proteínas morfogenéticas de osso e fatores de crescimento derivados de plaquetas podem ser encontrados no osso, cemento dentário e tecidos em cicatrização. Existem cerca de vinte no primeiro grupo, sendo produzidas por osteoblastos, plaquetas, condrócitos e células osteoprogenitoras. São capazes de estimular a sobrevivência e morte celular, a síntese e secreção de outros fatores vasculares e de osso, assim como induzir a formação de osso e cartilagem num processo que mimetiza o processo embrionário. O outro grupo anteriormente indicado é um potente mitogénio que promove a formação de colagénio e proteínas. É responsável pela estimulação da quimiotaxia de fibroblastos e de células musculares lisas.

Objetivo: O principal objetivo desta revisão foi avaliar os efeitos de implantes dentários com fatores de crescimento na sua superfície na osteointegração e formação de osso. Foram comparados os valores de contacto osso com implante, a estabilidade primária e a análise histolológica/histomoformética com recurso a fluorcromos entre os vários estudos selecionados.

Materiais e métodos: A pesquisa bibliográfica foi efetuada em três bases de dados electrónicas (PubMed, Evidence Based-Dentistry e Cochrane Library) com as palavras-chave: growth factors AND osseointegration AND dental implants", "bone morphogenetic protein AND osseointegration AND dental implants", "platelet derived growth factor AND osseointegration AND dental implants" durante o período de tempo de 1 de Novembro de 2016 até 31 de Maio de 2017. Os artigos foram limitados às línguas inglesa, portuguesa e espanhola. Foram considerados como critérios de inclusão apenas estudos in vivo, que avaliassem o efeito dos fatores de crescimento na superfície de implantes dentários na osteointegração de ossos maxilares e mandibulares. A pesquisa não foi restrita a nenhum período específico de tempo ou modelo de estudo. Relativamente aos critérios de exclusão, estes incluíam estudos in vitro, estudos que avaliassem o efeito na formação de osso com o recurso a outras biomoléculas ou outros tipos de osso e que utilizassem fatores de crescimento ou outros materiais no alvéolo dentário antes ou após a colocação do implante. Estudos sem grupos de controlo também foram excluídos. Os artigos foram inicialmente avaliados em bases de dados secundárias, através dos seus títulos e resumos. A literatura considerada relevante foi obtida e examinada para se identificar a sua importância para esta revisão. A pesquisa foi posteriormente estendida para bases de dados primárias com o mesmo processo de seleção. As referências bibliográficas também foram analisadas de modo a serem incluídos mais estudos. A pesquisa recolheu um total de 579, que após seleção foi reduzido para 76. No final, nove estudos animais foram incluídos nesta revisão.

Resultados: Um total de nove estudos animais foram analisados nesta revisão e organizados em tabelas segundo a modificação de superfície dos implantes e os resultados obtidos. Cinco dos estudos obtidos revelaram um efeito positivo dos fatores de crescimento na osteointegração, com valores de contacto osso-implante e quociente de estabilidade de implantes mais elevados em implantes de superfície modificada dos que estavam no grupo de controlo. Estas diferenças podem ser justificadas devido à influência

de parâmetros como a topografia da superfície, os modelos animais, a taxa de libertação da proteínas e processo de cicatrização. Diversos tipos de animais foram utilizados nomeadamente cães, macacos e porcos. Esta variação implica uma formação de osso diferente e por isso alteração dos valores obtidos. Para além disso, é necessário ter em consideração os diversos períodos de tempo na cicatrização e follow-up que variaram bastante. A falta de uniformização entre estudos relativamente a estes fatores pode ter influenciado a formação de osso e osteointegração. As proteínas morfogenéticas de osso são libertadas após colocação de implante e por isso a sua concentração e período de atuação é essencial. Estas proteínas têm uma semi-vida bastante curta, levando a que doses de maiores concentrações sejam necessárias. No entanto, a literatura disponível revela o efeito nefasto que este aumento de quantidade pode levar, com uma estimulação exagerada de osteoclastos e reabsorção óssea associada. Para aumentar a vida destas proteínas têm sido desenvolvidos sistemas de transporte que permitem que estas sejam libertadas de uma forma mais lenta através do uso de vetores ou implantes cuja superfície tenha fosfato de cálcio, entre outros. Os vetores de plasmídeos permitem a diferenciação de osteoblastos e células mesenquimais. Implantes com fosfato de cálcio parecem ter capacidade de osteoindução uma vez que permite a migração de células osteoprogenitoras ao longo da superfície de implantes, aumentando a osteogénese. Relativamente aos fatores de crescimento derivados de plaquetas, não é possível concluir a sua ação benéfica devido à falta de estudos in vivo associados a esta proteína. No artigo encontrado, observou-se uma extensa remodelação óssea imediatamente adjacente à superfície do implante.

Conclusão: A alteração da topografia das superfícies de implantes para formação de osso e proliferação de moléculas e células têm sido bastante estudadas. Os fatores de crescimento parecem ser uma opção de tratamento promissora uma vez que a literatura disponível mostra o seu efeito positivo na remodelação de osso e aumento da estabilidade primária. A maioria dos estudos selecionados demostram essa correlação com aumento dos valores de contacto entre osso-implante, quocientes de estabilidade de implantes e análise histológica com formação de novo osso. No entanto, as diversas variáveis entre os estudos, dificultam esta comparação e a formação de uma conclusão sobre a ação real destas proteínas. É essencial a criação de estudos prospetivos com follow-ups elevados para se perceber o verdadeiro papel destes fatores na osteointegração e consequentemente, a extrapolação desses resultados num modelo humano. A

uniformização de uma dose ideal e do seu efeito terapêutico é crucial para a sua aplicação clínica na medicina dentária.

Palavras-chave: fatores de crescimento, implantes dentários, osteointegração, proteínas morfogenéticas de osso, fatores de crescimento derivado das plaquetas

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LIST OF ABBREVIATIONS

%	Percentage
BIC	Bone-to-implant contact
BMP	Bone morphogenetic protein
BV	Bone volume
CaP	Calcium phosphate
CSA	Chromosulfuric acid surface-enhanced
HA	Hyaluronic acid
ISQ	Implant stability quotient
MAPK	Mitogen-activated protein kinase
PDGF	Platelet-derived growth factor
RFA	Resonance frequency analysis
rhBMP	Recombinant human bone morphogenetic protein
rhPDGF-BB	Recombinant human platelet derived growth factor-BB
SLA	Sand blasted and acid etched
TCP	Tricalcium phosphate
Ti	Titanium
TO	Titanium porous oxide

1. INTRODUCTION

The utilization of dental implants have gradually become a scientifically accepted treatment modality for the rehabilitation of fully and partially edentulous patients (Schenk & Buser, 1998). Implants are in fact one of the most successful treatments used in medicine and their survival rates are known to exceed 95% in most of the published long-term studies (Abuhussein, Pagni, Rebaudi, & Wang, 2010).

This progress is clearly based on the discovery that endosseous dental implants can be anchored in jaw bone with direct bone-implant contact (Schenk & Buser, 1998). Installation of implants elicits a sequence of healing events including necrosis and subsequent resorption of traumatized bone around the titanium body concomitant with new bone formation.

While the implant displays initial mechanical stability due to contact and friction between its surface and the bone, the long-term maintenance of implant stability calls for a biologic attachment between the foreign body and the surrounding tissue (Berglundh, Abrahamsson, Lang, & Lindhe, 2003). This direct structural and functional connection between living bone and implant surface, termed osseointegration, was first described by Brånemark and has undoubtedly been one of the most significant scientific breakthroughs in dentistry over the past 30 years (Esposito, Grusovin, Polyzos, Felice, & Worthington, 2010).

1.1 Osseointegration

Osseointegration has been defined from various viewpoints, including the description of long-term clinical results and the morphological appearance of the tissue-implant interface (Esposito, Hirsch, Lekholm, & Thomsen, 1998). One of the multiple definitions was given by Brånemark who describe it as a highly differentiated tissue making "a direct structural and functional connection between ordered, living bone and the surface of a load-carrying implant" (Mavrogenis, Dimitriou, Parvizi, & Babis, 2009).

Later, it was given a more clinical definition as a process in which clinically asymptomatic rigid fixation of alloplastic materials is achieved and maintained in bone during functional loading (Albrektsson, Johansson, & Sennerby, 1994).

Currently, an implant is considered osseointegrated when there is no progressive relative movement between the implant and the bone with which it has direct contact (Mavrogenis et al., 2009).

Osseointegration in clinical dentistry depends on an understanding of the healing and reparative capacities of hard and soft tissues (Brånemark, 1983). Bone healing around implants involves a cascade of cellular and extracellular biological events that take place at the bone-implant interface until the implant surface appears finally covered with a newly formed bone. Activated blood cells release growth and differentiation factors which are responsible for the regulation of this process (Mavrogenis et al., 2009).

After implantation, implant surfaces are in contact with body fluids and interact with different cell types (Zareidoost, Yousefpour, Ghaseme, & Amanzadeh, 2012). Blood and inflammatory cells emigrate from post-capillary venues and migrate into the tissue surrounding the implant. Consequently, they are activated and release cytokines and other soluble, growth and differentiation factors (Mavrogenis et al., 2009).

After haemostasis and clot formation, fibrinolysis occurs with the formation of a loose connective tissue stroma that supports angiogenesis (Cooper, 1998). The establishment of a well-vascularized, immature connective tissue, is proceed by the recruitment of osteoblasts and mesenchymal cells that attach to the implant surface and deposit bone-related proteins and create a noncollagenous matrix layer on the implant surface that mineralizes (Cooper, 1998; Mavrogenis et al., 2009).

This newly woven bone usually starts growing from the surrounding bone towards the implant where it is simultaneously deposited upon its surface. Bone deposition in this site increases the bone-implant interface and thus enlarges the load-transmitting surface (Schenk & Buser, 1998). Woven bone is progressively remodelled and substituted by lamellar bone that may reach a high degree of mineralization (Mavrogenis et al., 2009). This continuous process of bone modelling and remodelling is regulated by the local mechanical stress, as loading regulates proliferation and differentiation of osteoblasts and the bone healing process (Villar, Huynh-Ba, Mills, & Cochran, 2011).

1.2 Implant Stability

Successful osseointegration from the clinical standpoint is a measure of implant stability, which occurs after implant integration. It can be measured at two different stages: primary and secondary (Javed, Ahmed, Crespi, & Romanos, 2013).

Primary stability mostly occurs from mechanical attachment with cortical bone. Secondary stability offers biological stability through bone regeneration and remodelling (Meredith, 1998; Atsumi, Park, & Wang, 2007; Swami, Vijayaraghavan, & Swami, 2016). The first is dependent on the quantity and quality of bone, surgical technique and implant design. The latter depends on bone formation and remodelling at the implant-bone interface and is influenced by the implant surface and the wound-healing time (Quesada-García et al., 2009).

There are different devices that can be used to assess the stability of implants. (Kokovic, Vasovic, & Shafi, 2014). According to literature, these can be divided into non-invasive and invasive methods.

1.2.1 Invasive methods

These methods include histological/histomorphologic and removal torque analysis and pull and push-out tests (Swami et al., 2016).

The histological analysis helps calculate the peri-implant bone quantity and bone-implant contact (BIC) from a dyed specimen as well as the bone loss and the number of osteocytes present (Chai, Moharamzadeh, Brook, & Van Noort, 2011; Swami et al., 2016). The pull and push-out tests investigate the healing capacity at the bone implant contact. It measures interfacial shear strength by applying load parallel to the implant-bone interface (Swami et al., 2016). The removal torque is used for the measurement of initial stability between the samples and the host bone, because it determines the amount of force needed to destroy the interface (Yang et al., 2015). If is value is superior to 20 Ncm, the osseointegration is considered successful (Swami et al., 2016).

1.2.2 Non-invasive methods

It includes radiographs and resonance frequency analysis (FRA). Radiographs represent a generally accepted method to assess the long-term evaluation of interproximal crestal bone changes of osseointegrated implants. A clinically stable implant is associated with intimate contact with its implant surface. This can be detected radiographically (De Bruyn, Vandeweghe, Ruyffelaert, Cosyn, & Sennerby, 2013).

FRA is the most objective and reliable method of measuring the lateral micromobility of an implant during any stage of implant therapy. It uses a transducer that is fixed to the implant and vibrates when a piezoceramic element is used. This vibration produces a resonance frequency that changes according to the stiffness of the abutment-implant system (Park, Kim, Lee, & Lee, 2011). High frequency resonance indicates stronger bone-implant interface (Swami et al., 2016).The results are expressed as the implant stability quotient (ISQ) (Scarano et al., 2007).

1.3 Factors that influence osseointegration

Osseointegration is a process that is measured in clinical terms of implant fixture lifetime and this reflects the significance of lifelong functional maintenance of bone at the implant interface (Cooper, 1998). One of the determining factors of a successful clinical outcome is the rapid attachment of bone directly to the implant surface, providing anchorage to the mandibular or maxillary alveolar bone. This intimate structural relationship is vital to prevent the formation of peri-implant fluid filled spaces and the increase of the risk of infection that leads to implant failure (Colombo et al., 2012). According to Albrektsson, bone formation might be defined by six factors such as implant material, implant design, implant finish (surface), status of bone, surgical technique and the implant loading condition (Albrektsson, Brånemark, Hansson, & Lindström, 1981; Stadlinger, Pourmand, Locher, & Schulz, 2012).

Surface characteristics have been reported to significantly influence cell differentiation, local factor production and, consequently, bone growth and osseointegration (Gittens et al., 2011). After implantation, implant surfaces are in contact with body fluids and interact with a number of proteins and different cell types. The

challenge in the engineering of implant surfaces is to attract, above all, osteoblasts that produce a bone extracellular matrix, which will ensure a high bone-implant contact. It has been shown that osteoblastic cell adhesion, growth and differentiation are related to surface energy and roughness (Le Guehennec et al., 2008). Surface modification strategies for metallic implants to improve osseointegration have attempted to mimic the characteristics of bone (Gittens et al., 2011).

To enhance bone implant osseointegration, many strategies for improving biomaterial properties have been developed and include optimization of implant material, implant design, surface morphology and osteogenetic coatings namely peptide sequences, growth factors or osteoinductive proteins (Fini et al., 2004; Yoo et al., 2014).

1.4 Growth Factors

The rate of osseointegration is dependent on the commitment, replication, and differentiation of osteoprogenitor cells and on interfacial tissue maturation (Chang, Lang, & Giannobile, 2010).

Modification of the surface properties of the implants have successfully increased the bone-to-implant contact (Öncü, Bayram, Kantarci, Gülsever, & Alaaddinoglü, 2016). Osseointegration of dental implants can be improved and accelerated by inducing the regenerative capacity of surrounding tissues with the appropriate stimuli (Anitua, 2006). A strategy to reduce the osseointegration time has been the modulation of the healing response after the implant placement. This has been accomplished by biologically active molecules during implant placement to induce osteoconductivity, increase osteoblastic differentiation and enhance healing of peri-implant bone (Öncü et al., 2016). Growth factors are expressed during different phases of tissue healing and it has been thought that they could serve as therapeutic agents to promote tissue (Anitua, 2006).

Growth factors may be defined as agents that promote cell proliferation and metabolism by binding to specific cell surface receptors which transduce signals to the cell nucleus via complex signal transduction pathways (Kiritsy, Lynch, & Lynch, 1993;

Giannobile, 1996). These proteins may induce the migration of cells into the wound space, serving as chemoattractants to recruit important cells such as leukocytes and fibroblasts into the wounded area (Kiritsy et al., 1993). They are part of critical functions as cell division, matrix synthesis, tissue differentiation, chemotaxis and osteogenesis (Giannobile, 1996; Lieberman, Daluiski, & Einhorn, 2002; Chang et al., 2010).

Examples of growth factors found in bone, cementum and healing tissues include platelet-derived growth factor (PDGF) and the bone morphogenetic proteins (BMPs) (Giannobile, 1996; Devescovi, Leonardi, Ciapetti, & Cenni, 2008).

1.4.1. Bone Morphogenetic Proteins

Bone morphogenetic proteins are multi-functional growth factors that belong to the transforming growth factor b superfamily. The roles of BMPs in embryonic development and cellular functions in postnatal and adult animals have been extensively studied in recent years (Chen, Zhao, & Mundy, 2004).

In vertebrates, BMP genes are expressed in many embryonic organs and tissues, including those in which reciprocal interactions between epithelial and mesenchymal cells are important for morphogenesis and differentiation (Hogan, 1996).

The study of BMPs began in the 1960s, with the observation that demineralized bone matrix had the capacity to induce endochondral bone formation in subcutaneous and intramuscular pockets in rodents. Subsequently, it was isolated a low molecular weight glycoprotein from bone and demonstrated that it promoted bone formation when ectopically located (Granjeiro, Oliveira, Bustos-Valenzuela, Sogayar, & Taga, 2005).

Around twenty different proteins have been named BMP in humans, but not all members are truly osteogenic. The bone-inducing BMPs can be divided into several subgroups, according to homology of their amino acid sequences. BMP-2 and BMP-4 comprise one subgroup; the second group consists of BMP- 5, BMP-6, BMP-7 and BMP-8, while BMP-9 and BMP-10 form the third osteogenic group (Lissenberg-Thunnissen, de Gorter, Sier, & Schipper, 2011).

BMPs consist of dimers whose chains are connected by disulphide bonds and this dimerization is a prerequisite for bone induction. BMPs are active both as homodimer (two identical chains) and heterodimer (two different chains) molecules (Granjeiro et al., 2005). They are produced by osteoprogenitor cells, osteoblasts, chondrocytes and platelets. After their release, the extracellular matrix functions as a temporary storage (Lissenberg-Thunnissen et al., 2011).

BMPs are capable of inducing ectopic cartilage and bone formation, a process that mimics embryonic endochondral bone formation and includes chemotaxis and mitosis of mesenchymal cells, differentiation of the mesenchymal cells initially into cartilage, and replacement of the cartilage by bone (Li et al., 2003; Xiao, Xiang, & Shao, 2007). In addition, they also regulate haematopoiesis, stimulate extracellular matrix synthesis, and influence cell survival maintenance and cell death (apoptosis) (Li et al., 2003). These proteins stimulate the synthesis and secretion of other bone and angiogenic growth factors such as insulin-like growth factor and vascularendothelial growth factor (Dimitriou, Tsiridis, & Giannoudis, 2005).

The regulatory effects of BMPs depend upon the target cell type, its differentiation stage, the local concentration of BMPs, as well as the interactions with other secreted proteins (Lissenberg-Thunnissen et al., 2011).

BMPs bind to serine/threonine kinase receptors that are composed of a short extracellular domain with 10–12 cysteine residues, a single transmembrane domain, and the intracellular serine/threonine kinase domain (Dimitriou et al., 2005; Bragdon et al., 2011). These receptors are named type I or II and both are required for signal transduction. Type I receptors are activated by Type II receptors following BMP binding. This interaction initiates the Smad intracellular signalling cascade or mitogen-activated protein kinase (MAPK) cascade (Tsiridis, Upadhyay, & Giannoudis, 2007; Wu, Chen, & Li, 2016).

The BMPs signal transduction is mainly mediated via the classical BMPs–Receptor–Smads signal pathway. The activation of the BMPs-MAPK can transduce the signal into nuclei via JNK-1 and 2/3, ERK1/2, NF-B and p38 signal pathways where they regulate the expression of target genes and play their biological roles. This signal transduction pathway plays important role in BMP-induced osteogenesis (Yang et al., 2015).

Smad proteins are ubiquitously expressed in chondrocytes during the entire process of chondrogenesis (Song, Estrada, & Lyons, 2009). Nuclear accumulation of these molecules was observed in proliferating and maturing chondrocytes (Sakou et al., 1999).

The osteoinductive capacity of BMP has been demonstrated in preclinical models and evaluated in clinical trials (Chen et al., 2004).

1.4.2. Platelet-Derived Growth Factor

PDGF is a potent mitogen and chemotactic factor for cells of mesenchymal origin, including periodontal ligament cells, and osteoblasts (Chang et al., 2010).

It is a dimeric cationic, heat stable protein stored in the alpha granules of circulating platelets (Lynch, Nixon, Colvin, & Antoniades, 1987; Cury & Guimarães, 2012). Platelets are the largest source of PDGF but activated macrophages and fibroblasts also secrete it (Hosgood, 1993). The platelet is the first cell at the site of the injury coincident with haemorrhage and play an important role in initiation and progression of wound repair, from inflammation to resolution through collagen remodelling (Deuel, Kawahara, Mustoe, & Pierce, 1991; Hosgood, 1993).

PDGF has a half-life of approximately thirty minutes when circulating in the blood, suggesting that local delivery of the growth factor will be critical to achieving clinical success (Hollinger, Hart, Hirsch, Lynch, & Friedlaender, 2008).

Platelet-derived growth factor interacts with its target cells by noncovalent binding to a cell surface receptor that has a high affinity and selectivity for them. These receptors have been identified in fibroblasts, smooth muscle cells, glial cells and chondrocytes. The two chains of the PDGF dimers bind to the receptor molecule, resulting in the dimerization of the receptor subunits that is required for transmission of the mitogenic signal (Hosgood, 1993). Another prerequisite for the role of PDGF in wound healing is that cells in the wounded area express PDGF receptors (Heldin & Westermark, 1999).

PDGF is also chemotactic for fibroblasts and promotes collagen and total protein synthesis. It stimulates gingival fibroblast hyaluronate synthesis, a prerequisite for the formation of large aggregates of proteoglycans that provide the lattice for the

extracellular matrix (Giannobile, 1996). PDGF stimulates collagenase activity and chemotaxis of fibroblasts and smooth muscle cells (Lynch et al., 1987).

2. OBJECTIVES

The aim of this review is to evaluate the effect of growth factors coating dental implants on the osseointegration and to analyse the potential benefit of their use on the formation of bone and implant stability.

The principal parameters of comparison were the contact of bone to implant, the implant stability quotient values and histological/histomorphometric analysis using fluorochromes at different periods of healing.

3. MATERIALS AND METHODS

3.1 Research methods

An electronic search was conducted in three databases (PubMed, Evidence Based-Dentistry and Cochrane Library) with the keywords “growth factors AND osseointegration AND dental implants”, “bone morphogenetic protein AND osseointegration AND dental implants”, “platelet derived growth factor AND osseointegration AND dental implants, during November the first of 2016 until May thirty-first of 2017. Articles were limited to those published in English, Portuguese and Spanish.

3.2 Inclusion criteria

- In vivo studies
- No restricted period of time
- Dental implant surfaces coated with growth factors
- Evaluation of the effect on osseointegration after implant placement
- Placement of dental implants in maxillae or mandibular bone

3.3 Exclusion criteria

- In vitro studies
- Filling of the dental socket with growth factors or other materials before or after implantation in order to promote bone formation
- Use of other bioactive molecules coating the surface of dental implants
- Placement of dental implants in other types of bone
- Studies that did not compared coated with uncoated (control group) surfaces

3.4 Data Collection Process

The articles were firstly selected on secondary databases, according to theirs titles and abstracts. The literature considered important was obtained and examined to

identify its relevance and inclusion of the mentioned criteria. The research was subsequently extended to primary databases with the same method of selection.

Reference lists of the studies were analysed in order to identify additional literature relevant for this review.

The search yielded a total of 579 studies that after selection was reduced to 76 articles. At the end, nine animal studies were included.

4. RESULTS

A total of nine animal studies were analysed in this review. After an extensive search in the electronica databases previously mentioned and considering the inclusion and exclusion criteria, the articles were selected and organized in tables divided by the type of surface modification and the results obtained.

4.1 Dental implant surfaces coated with BMPs

Author, Year	Surface modification	Results
KIM, 2015	SLA uncoated implants - control SLA + rhBMP-2 (0.1mg/mL) SLA + rhBMP-2 (0.5mg/mL) SLA + rhBMP-2 (1mg/mL)	**BIC values %** <u>Buccal area:</u> **Control:** 0.67±1.15 **rhBMP-2 (0.1mg/mL):** 10.24±10.99 **rhBMP-2 (0.5mg/mL):** 24.47±6.63 **rhBMP-2 (1 mg/mL):** 18.42±8.65 <u>Lingual area:</u> **Control:** 23.37±7.08 **rhBMP-2 (0.1mg/mL):** 26.50±10.97 **rhBMP-2 (0.5mg/mL):** 35.45±7.16 **rhBMP-2 (1 mg/mL):** 33.43±11.39 **ISQ values** **Control:** 60.17±3.25 **rhBMP-2 (0.1mg/mL):** 64.83±3.19 **rhBMP-2 (0.5mg/mL):** 71.67±6.15 **rhBMP-2 (1 mg/mL):** 72.00±2.68

HE, 2013	SLA uncoated implants - control SLA implants coated with rhBMP-2 plasmids	**BIC values %** Control: 48.68 Coated implants: 55.67
HUNZIKER, 2012	1. SLA 2. CaP 3. RhBMP-2 4. CaP + rhBMP-2 incorporated 5. CaP + rhBMP-2 adsorbed 6. CaP + rhBMP-2 incorporated and adsorbed	**Week 1:** highest volume fraction in groups 4 and 5 **Week 2:** groups 3 and 4 **Week 3:** group 3 and 4
HUH, 2012	Uncoated + anodized implants - control Coated with rhBMP-2	**BIC values %** **Control:** 40.16 ±23.77 **rhBMP-2:** 41.88±22.71 **ISQ values** **Control:** 74.27±6.67 **rhBMP-2:** 79.21±3.11

WIKESJÖ, 2008	TPO uncoated implants – control TPO coated with rhBMP-2 (2.0 mg/ml) TPO coated with rhBMP-2 (0.2 mg/ml)	**BIC values %** **Control:** 75% **rhBMP-2 (2.0 mg/ml):** 43% **rhBMP-2 (0.2 mg/ml):** 37%
WIKESJÖ, 2008	TPO uncoated implants – control TPO coated with rhBMP-2 (4.0 mg/ml) TPO coated with rhBMP-2 (0.2 mg/ml)	**BIC values %** **rhBMP-2 (4.0 mg/ml)** 35.4 **vs Control** 68.2 **rhBMP-2 (0.2 mg/ml)** 43.3 **vs Control** 71.7

LIU, 2007	1. Ti 2. Ti+ rhBMp-2 adsorbed 3. Ti+CaP 4. CaP + rhBMP-2 incorporated 5. CaP + rhBMP-2 adsorbed 6. CaP + rhBMP-2 incorporated and adsorbed	Bone volume was highest for CaP and titanium and lowest for CaP + rhBMP-2 adsorbed Bone coverage was highest for CaP and lowest for Ti+ rhBMp-2 adsorbed
BECKER, 2006	SLA CSA CSA+ rhBMP-2 (596 ng/cm2) CSA+ rhBMP-2 (819 ng/cm2)	**BIC VALUES** rhBMP-2 (819 ng/cm2) > rhBMP-2 (596 ng/cm2) > CSA > SLA

TABLE 1. Dental implant surfaces coated with bone morphogenetic proteins

Kim (Kim, Lee, Ryu, Choi, & Huh 2015) investigated the influence of rhBMP-2 on the osseointegration of implants in four beagle dogs for eight weeks. Twenty four implants made of pure titanium were sand blasted with large grit and acid etched. For the coating, each implant was immersed in a protein solution (0.1, 0.5 and 1.0mg/mL). The control group had no coating on its surface. All the dogs were submitted to a first surgery in which the mandibular premolars and first molars were extracted. Two months later, the surgical placement of dental implants was performed.

The results were presented according to the implant stability quotient and the bone mineral deposition. ISQ values were recorded immediately after implantation and at the end of the study. There was no significant difference in the ISQ values among groups after the implant surgery. At the last week, it was observed that the rhBMP-2 coated implants showed greater values when compared to the control group, being the highest the 1.0 group.

The new bone formation was measured by the fluorochromes calcein (green) at two weeks and alizarin red s (red) at six weeks. The control group showed no notorious difference in time, unlike the other groups were bone deposition and remodelling was observed.

The bone-to-implant contact and the bone volume were measured and it was observed greater values for the rhBMP-2 groups when compared to the control group. It was also noted that the buccal defect areas presented higher percentages that the lingual areas.

The percentage of rhBMP-2 released was determined by the ELISA test. It was observed that 90% of the 0.1 and 0.5 groups and 70% of the 1.0 group was released in the first six hours. After four days, all the concentration of this grow factor was released.

He (He, Shan, Shen, & Jiang, 2013) conducted a study in which twelve beagle dogs were subjected to the extraction of all the premolars and molars of the lower jaw and implant surgery three months later. There were two groups comparing the effect of BMP-2: a control group that was uncoated and the other had rhBMP-2 plasmids on the surface (coated by using a transfection reagent).

The histological samples were examined to observe the formation of peri-implant, woven and lamellar bone by using an incandescent light microscopy. At week eight, new bone

around the implant and its transformation into lamellar bone as well as remodelling of old bone was noticed.

The BIC values increased in both surfaces and were higher in the coated implants at the end of the study. However, the change between groups was not significant.

The implant stability was also measured using the removal torque analysis. At twelve weeks, the values were similar (coated implants - 81 vs uncoated – 77). The removal torque values were lower at the beginning of the study (4 weeks) with no difference between the last weeks (weeks eight and twelve).

Hunziker (Hunziker, Enggist, Küffer, Buser, & Liu, 2012) studied the different BMP-2 delivery modes and its efficacy in eighteen miniature pigs. Six experimental groups were established: implants bearing a calcium-phosphate coating into which BMP-2 was incorporated, superficially adsorbed or both, implants bearing a coating but no BMP-2, implants bearing no coating but a superficially adsorbed depot of BMP-2 and implants bearing neither a coating nor a depot of BMP-2 (control group).

In the groups in which implants bore either a coating-incorporated, a coating-adsorbed, or both a coating-incorporated and a coating-adsorbed depot of BMP-2, the fraction of mineralized bone increased during the three weeks of the study.

Among the other groups (implants bearing a coating alone, implants bearing a directly-adsorbed depot of BMP-2 and implants bearing neither a coating nor a depot of BMP-2), the unmineralized bone increased in the first week and decreased in the rest of the study.

At the week two and week three, the volume fraction of mineralized bone was highest in association with implants that bore a coating-incorporated depot of BMP-2 and lowest with those that bore a coating-adsorbed depot of the osteogenic agent or both a coating-incorporated and a coating-adsorbed depot of BMP-2.

Six beagle dogs were subjected to the extraction of all the premolars and molars in Huh's study (Huh et al., 2012). Two months after complete healing, thirty-six anodized implants coated with ErhBMP-2 or without (control group) were installed randomly.

During eight weeks, the ISQ values were measured in each implant. Immediately after surgery, the difference between groups was not statistically relevant. At the end of the

study, the values were higher for the BMP group whereas in the control group the chance was barely noticeable.

Regarding the bone level, it was visible the formation of bone and consequently the BIC percentages were higher for the coated implants. However the difference was not statistically significant when both groups were compared.

Wikesjö (Wikesjö et al., 2008) studied the evaluation of local bone formation and osseointegration using rhBMP-2-coated implants in eight monkeys for sixteen weeks. There were three groups comparing this process: a control group with uncoated implants, a group with rhBMP-2 (0.2mg/ml) and another with rhBMP-2 (2.0mg/ml). Each animal received three coated implants in one quadrant and three uncoated in the contra-lateral quadrant as control.

At the end of the study, the higher percentages belonged to the uncoated implants. The first surfaces presented a thin layer of bone covering most of the implant threads which lead to a high-level bone–implant contact.

The same author (Wikesjö et al., 2008) conducted a similar study where he observed the influence of the same growth factor in eight dogs whose all premolars and first lower molars were extracted. The animals were subjected to an implant surgery with uncoated or coated implants with rhBMP-2 (0.2mg/ml; 4.0mg/ml).

The placement of implants and posterior sutural removal was characterized by a pronounced swelling at the sites with the coated implants (4.0mg/ml). The reaction was less exuberant in the other groups.

Bone formation and remodelling was observed adjacent to the implant surface in a higher scale for the control group as the coated implants appeared to have lower BIC values.

Fluorescent bone markers were used at different times namely the narrow oxy-tetracycline (week three), xylenol orange (week four) and calcein green (week eight). It was observed rapid bone formation (week three and four) for implants coated with rhBMP-2 (0.2mg/ml). RhBMP-2 (4.0mg/ml) presented extensive bone formation within and immediately outside the thread area from week two through four, with little bone formation at week eight. This concentration exhibited markedly increased bone metabolic activity compared to the other group.

Liu (Liu, Enggist, Kuffer, Buser, & Hunzinker, 2007) studied the the influence of BMP-2 and its mode of delivery on the osteoconductivity of sand-blasted and acid- etched titanium surfaces and of surfaces that bore a coating of calcium phosphate. Six groups were established: groups that consisted of titanium implants that were biomimetically coated with a layer of calcium phosphate bearing either incorporated, adsorbed or no BMP-2 and uncoated titanium implants bearing either adsorbed BMP-2 or no BMP-2.

The total of bone deposited within the osteoconductive space of the implant chambers was the lowest in the two uncoated implants and lower in the presence of BMP-2, in the first week of the study. At the second week, the bone volume associated with uncoated implants was still lower in the presence of this growth factor. In the last week, all the groups presented an increase of bone volume except in the group with the incorporated and adsorbed BMP-2.

The bone coverage of the coated implants bearing no BMP-2 presented the highest values. Similarly, on the uncoated implants the greatest results belonged to the surfaces with no BMP.

Becker (Becker et al., 2006) extracted all the lower premolars and first molars of two mongrel dogs and proceeded to the placement of rhBMP-2-biocoated (two concentrations: 596 ng/cm^2 and 819 ng/cm^2) and uncoated implants (two groups: sandblasted and acid-etched and chromosulfuric acid surface-enhanced) four months later.

All coated and uncoated implants exhibited new bone formation in direct contact with the implant interface and organized trabeculas of woven bone. This process seemed to be higher in the BMP groups. The BIC values were greatest to the group with the higher BMP concentration and the lowest for the sandblasted implants.

4.2 Dental implant surfaces coated with PDGFs

Author, Year	Surface modification	Results
AL-HEZAIMI, 2014	Uncoated implants – control Coated with rhPDGF-BB Coated with prototype viscous rhPDGF-BB	**BIC values %** **Control:** 58.7±4.1 **rhPDGF-BB:** 78.0±12.5 **Prototype viscous rhPDGF-BB:** 59.4±17.6

TABLE 2. Dental implant surfaces coated with platelet derived growth factors

Al- Hezaimi (Al-Hezaimi, Nevins, Kim, Fateh, & Kim, 2014) conducted an experiment with six beagle dogs to understand the efficacy of rhPDGF-BB on the promotion of early osseointegration. In order to achieve this, three groups were created: a control with uncoated implants and two coated with the growth factor (rhPDGF-BB and prototype viscuous rhPDGF-BB).

At week three it was observed new bone forming between most of the implant threads of the coated implants, with a thin amount of bone on the uncoated. At the end of the study, it was showed that the rhPDGF-BB coated implants present higher BIC values when compared to the other groups.

4.3 DISCUSSION

Surface properties play a key role in biological interactions between the implant surfaces and the host bone. Modifying surface roughness has been shown to enhance BIC and improve the clinical performance of implants (Anil, 2011).

The rate of osseointegration is dependent on the commitment, replication, and differentiation of osteoprogenitor cells and on interfacial tissue maturation. Since growth

factors, such as BMP and PDGF, enhance osteogenesis, they were suggested to accelerate peri-implant wound healing and osseointegration (Chang et al., 2010).

The objective of this review was to evaluate the effect of dental implants coated with these proteins on osseointegration. Nine articles were analysed that studied the process of bone formation and the intimate contact of bone and implant. In order to assess the results, the BIC and ISQ values were measured as well as histological examination using fluorochromes at different times.

Five out of nine studies reported a positive effect on osseointegration and bone formation. Among these studies, it was noted that the BIC values were higher for the coated implants. For example, Kim et al. (Kim et al., 2015) showed the greatest difference between uncoated and coated with a value of 0.67 and 24.47, respectively.

Moreover, when the stability was regarded, the ISQ results were similar as the BMP or PDGF coated implants were characterised by greater percentages, thus reinforcing the positive effect of these growth factors on the osseointegration of dental implants. As an example, the study of Huh (Huh et al., 2012) showed a change of 9.29 during the period of the study compared to the 0.27 for the uncoated group.

Regardless of the positive effects, some studies revealed a negative connection to the use of BMPs in the promotion of an early osseointegration. Wikesjö (Wikesjö et al., 2008) in both of his studies demonstrated that the coating of implants was not beneficial. Even using the highest concentration of these proteins, the values of the group control were greater (75% versus 43% for the study with the monkeys and 68.2% versus 35.4 in the dogs' study).

The different values regarding the BIC or ISQ values can be explained by the influence of various factors such as the topography surface of the implants, the animal models, the rate of release of the molecules, the process of healing and the location.

Different animal models were used in the studies, which implies different dynamics of bone formation especially in early healing intervals and consequently the variance of values observed for the BIC (JENNY, 2016). For example, Wikesjö (Wikesjö et al., 2008) obtained various values using different animal models (monkey vs dog) in

similar conditions. This discrepancy can also be justified by the different quality of bone used in both studies (type II and type IV).

It is important to consider the process of healing as a factor of discrepancy since the period of time was different among studies and may have influenced the results. Some authors waited two months after placing the implants as seen in Kim (Kim et al., 2015) while others only performed the surgery four months later like Becker (Becker at al., 2006). Longer periods of healing can influence the formation and remodelling of bone.

The lack of standardization in the conditions in which the animals were subjected during the healing phase could have also contributed. Some articles mentioned the process during this time while others didn't report it. The follow up was different and varied from three weeks (Hunzinker et al., 2012) to eight weeks (Huh et al., 2012) and it could have influenced the quantity of bone formed and release of BMP-2.

When compared to humans, the dogs are the animal with the major resemblances in bone anatomy. While there are structural similarities in trabecular and cortical bone, the turnover rates in dogs are found to be highly variable between bone sites (Pearce, Richards, Milz, Schneider, & Pearce, 2007). Consequently, the difference in results between animals can be explained by it and why it is important to consider this factor when conducting the same studies in humans.

It is also interesting to observe the results of studies that examine the effects on other types of bone. Lan (Lan, Wang, Shi, Xia, & Cheng, 2007) subjected eight rabbits to an implant surgery on the femur. Each animal received an implant uncoated and other coated with rhBMP-2. At twelve weeks, the higher percentage of total bone belonged to the coated group (15%) in comparison to the 11% of the control group. The pull-out test showed a statistically greater strength for the BMP-2 (36.5±2.02N vs 27.63±1.31N).

In Torey's study (Torey et al., 2011), eight rabbits were divided in four groups after implant placement on the femoral condyle of both hind legs. They were divided in four groups, two of them uncoated and two coated with BMP-2. The results indicated higher values of bone ingrowth and pull-out strength for the coated implants when compared to all the other groups.

These studies contribute to support the positive effect of BMPs, even in other types of bone.

The location and the size of the defects were another factor that could have influenced the results. The differences values on Kim's study (Kim et al., 2015) prove this point. It was observed that the BIC values in the lingual area were higher than those in buccal (26.50% vs 10.24%). This could be explained by the larger size of the buccal effect that lead to a lower formation of bone.

Different techniques are available to incorporate these proteins into metallic implants. A simple method is a direct adsorption whereby the growth factor is adsorbed to the surface through non-covalent interaction. The main disadvantage of this process is the low retention time and inconsistent release profile (Zhang, Myers, Wallace, Brandt, & Choong, 2014).

In the studies analysed, it was observed various implant surfaces as pure or porous titanium, sand blasted and acid etched, calcium phosphate or anodized. According to literature, an oxidized layer plays a role on the activation of cells on a titanium surface (Huh et al., 2012). The anodic-oxidized surface has an inherent photocatalytic activity, which can enhance osseointegration and increase the initial healing process (Mishra, Kumar, & Chowdhary, 2017). Porous surfaces are able to provide biological anchorage for the surrounding bone tissue via the ingrowth of mineralized tissue into the pore spaces (Vasconcellos, Leite, Oliveira, Carvalho, & Cairo, 2010). Roughening the titanium surface induces an excellent bone cell response to the surface. It can be roughened by blasting, acid etching or by a combination of the two. Superior histomorphometry and stronger bone responses have been found on roughened surfaces compared to turned surfaces as well as greater resistance to removal torque (Yeo, 2014). The blasted implants present a significantly longer bone implant interface than smooth ones and consequently cell stay longer on those surfaces (Piattelli, Manzon, Scarano, Paolantonio, & Piatelli, 1998). Calcium phosphate coating seems to be osteoconductive as it promotes migration of osteoprogenitor cells along its surface and, therefore, accelerates osteogenesis (Yang, 2001). Adsorbed osteogenic molecules bind with higher affinity to calcium-phosphate implant coatings than to the naked metallic surface (Liu et al., 2007). The porosity of the calcium phosphate is a critical factor that affects the osteoinductivity of coatings. In rat models of osteoinduction, the bone formation is maximal when the pore size of the

scaffolds is within 300-400μm as it relates to the reduced vascular infiltration and oxygen levels on small sizes (Zhang et al., 2014). All of these factors are responsible for the different values obtained among studies.

Controlled release of BMP-2 with an appropriate time period and concentration is a prerequisite to effectively accelerate bone regeneration (Yang et al., 2015). It is crucial to standardize an ideal dose of rhBMP-2 for each of the different implant surfaces (Kim et al., 2015). These proteins have a short half-life and for a successful result is it necessary a high dose (He et al., 2013).

In order to optimize its efficacy and release rate, a variety of biomaterials and systems have been investigated, denominated as carriers. A carrier should ideally induce an optimal inflammatory response, should be completely biodegradable, present adequate porosity for infiltration and proliferation of cells and sprouting blood vessels at the site of new bone formation and prevent degradation of BMPs (Sheikh, Javaid, Hamdan, & Hashmi, 2015). An example seen in one of the studies analysed was of a liposomal vector. According to literature, DNA plasmids are able to promote osteogenic differentiation of osteoblasts and mesenchymal stem cells (Zhang et al., 2014). The results from it, however, were not significant. This could be explained by the creation of antibodies against the protein and the cytotoxicity of the reagents used. A similar study was conducted by Jiang (Jiang et al., 2013) where fifteen white rabbits were subjected to the placement of BMP-2 gene coated implants on their femurs. After eight weeks, it was observed that the coated implants presented a BIC value of 41.5 ± 7.3%, in contrast to the 45.9 ± 17.4% of the uncoated surfaces.

The release profile of BMP-2 can also be improved by being incorporated using heparin since it contains biding sites for it at its basic N-terminal. This binding promotes osteoblast differentiation and extends the retention time of it (Zhang et al., 2014). It also protects the protein from degradation as it decreases the binding of noggin, a potent inhibitor of BMP-2 (Yang, Moon, & Lee, 2017). A study from Yang (Yang et al., 2015) demonstrated that the use of this carrier can be advantageous in the promotion of osseointegration because it presented higher BV and BIC values than the pristine titanium surfaces. Sixteen white rabbits were subjected to a femur and proximal tibia surgery and were implanted different types of implants (Ti; Ti+hydroxyapatite; Ti+heparin+BMP-2; Ti+hydroxyapatite+heparin+BMP-2). After four weeks, it was noted that the pure

implants presented a BIC value of 35.7% in comparison to the 49.8% of BMP-2 coated implants. The ISQ values revealed also the positive effect of this carrier (0.5 vs 2.7). In a more recent study using a heparin linker from Yang (Yang et al., 2017), it was compared among others the pristine titanium and rBMP-2 surfaces. The BIC values for the uncoated were 21.4% in contrast to the 38.8% and the ISQ values were 0.2 and 2.8, respectively. The histological samples of both studies showed enhanced bone formation and remodelling at the interface of the implants. BMP-2 was released during the study in a sustained way.

Apart from heparin and liposomal vector systems, other BMP-2 carriers that have been studied include inorganic materials as tricalcium phosphate (TCP) combined with hyaluronic acid (HA) and nanotube arrays.

Lee (Lee et al., 2014) analysed inorganic carriers and their ability to slow the rate release of BMP-2. TCP microspheres and HA based power gel were used to demonstrate this effect. TCP is structurally similar to the bone and HA is one of the major components of the extracellular matrix which plays an important role in tissue organization, angiogenesis and wound healing. In this study, seventeen white rabbits were allocated in three groups (implant; hydrogel; hydrogel+BMP-2) after tibia surgery. The results showed a BIC ratio of 8.3± 2.1 %, 7.6 ± 3.8 % and 23.2 ± 6.4 % respectively, showing a significantly higher value for the BMP-2 group. In the histological analysis, the group of the growth factor present strong osseointegration in the cortical bone and the formation of newly bone.

Lee (Lee, Choi, Jang, & Choi, 2015) used titanium dioxide nanotube arrays in order to immobilize the rhBMP-2 enough time to promote osseointegration. The nanotubes have a good oxide structure that can influence protein interactions and components of bone. These arrays were formed on the surface of dental implants and provided empty spaces for the proteins. The group with the growth factor presented higher values of BIC and BV than the other surface modifications (BIC: 29.5±3.8 %, BV: 77.3±8.8; Machined surface – BIC: 11.1±17.0%, BV: 66.9±6.7; SLA surface - BIC: 14.7±9.5%, BV: 53.7±11.5; Nanotube only surface - BIC: 16.3±11.9%, BV: 67.2±7.6).

The excessive dose can also cause side-effects, such as bone overgrowth, ectopic bone formation and immune responses (Yang et al., 2015; Lee et al., 2015). In Liu's study, (Liu et al., 2007), when BMP-2 was available in both in an incorporated and

adsorbed form, the amount of release of this protein was higher than in other forms. As a consequence, the volume of bone formed was lower and could be explained by the fact that its high concentration might have overstimulated the bone-resorption activity of osteoclasts. Similar results were experienced in Hunziker's study (Hunziker et al., 2012).

All that was mentioned previously is according to the evidence of the studies that involved BMPs coated implants. As only one article was found about the PDGF, it is not possible to come to a conclusion for the beneficial effect of this growth factor. The results are characterised by a marked bone remodelling with island of native bone in the immediate vicinity of the implant surface (Al-Hezaimi et al., 2014).

In summary, this review presented the influence of growth factors coating implant surfaces on the promotion of osseointegration and therefore their contribution to the implant stability and success long term.

Although the majority of the studies demonstrated a positive effect of growth factors on the formation of bone, their small samples sizes and various variables make the comparison of studies and their analysis difficult. Therefore, it is not possible to conclude that the coating of implants with the molecules can increase the rates of osseointegration. The articles available compared different concentrations of the proteins, types of implants surfaces and animal models thus contributing to the diverse range of values.

These results might not be extrapolated to human groups due to all the differences between animals and humans in terms of anatomy, systemic diseases and patient behaviour. Therefore, it is important the creation of well-designed prospective studies in order to assess the real effects of growth factors on the remodelling of bone and their optimal dose for the maximum results. These studies should have a uniformed experimental protocol with specific criteria to make the comparison of results more effective.

The coating of dental implants with growth factors seems to be a promising alternative to increase the rate of long term successful implant surgeries and needs to be assessed in order to become an available option for future treatments.

5. CONCLUSION

The endosseous dental implant has become a scientifically accepted option of treatment for fully or partially edentulous patients. In order to increase the success of this modality, various studies have been developed to enhance osseointegration and an intimate contact between bone and implant.

New technologies are altering the topographic surface of implants to promote the formation of bone and the proliferation of cells and molecules that enhance the healing.

Growth factors coating the implants have been a promising option as available literature demonstrates their positive effect on the remodelling of bone and increase of primary stability.

In the majority of the studies it was observed a beneficial influence of these molecules on the bone. However, the different variables make it difficult to make a conclusion about their effect on osseointegration.

It is crucial the creation of long term prospective studies involving human models to understand the real consequences of growth factors on the formation of bone.

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